General

Guideline Title

Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA 142).

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142). London (UK): National Institute for Health and Care Excellence (NICE); 2014 Nov. 47 p. (Technology appraisal guidance; no. 323).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 36 p. (Technology appraisal guidance; no. 142)

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cancer treatment-induced anaemia

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Hematology

Internal Medicine

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of epoetin alfa, beta, theta and zeta, and darbepoetin alfa for cancer treatment-induced anaemia

Target Population

Patients with anaemia induced by cancer treatment

Interventions and Practices Considered

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa)

Major Outcomes Considered

- Clinical effectiveness
  - Anemia-related outcomes including haemoglobin change, red blood cell transfusion requirements, number of units transfused per patient, and haematological response
  - Malignancy-related outcomes including tumour response and overall survival
  - Health-related quality of life
  - Safety-related outcomes including number of adverse events, number of serious adverse events, and thromboembolic events
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Identification of Studies

The search strategy is based on the strategy used in the previous multiple technology appraisal (MTA) on this topic by Wilson and colleagues (2007)†. It combines free-text and medical subject headings (MeSH) terms for epoetin (generic and brand names), cancer and anaemia using the AND Boolean operator. Search filters are applied to retrieve randomised controlled trials (RCTs), cost effectiveness studies and quality of life studies. The search terms and structure of the search is mainly the same as in the previous MTA, with additional search terms for epoetin theta, epoetin zeta and corresponding drug brand names. The search filters for RCTs, cost effectiveness studies and quality of life (QoL) studies are different to those used previously. The filters were developed by an information specialist to ensure an appropriate balance of sensitivity and specificity. Changes to the previous MTA search strategy, including the filters, were made in MEDLINE and translated as appropriate for other databases. The MEDLINE RCT search strategy was checked by a clinical expert for inaccuracies and omissions relating to drug and cancer terms.

The databases were searched from the search end-date of the previous MTA on this topic (search end-date: 2004). Although epoetin alfa (Binocrit®), epoetin theta and epoetin zeta were not covered in the previous report, the Assessment Group believes that relevant interventional research is highly unlikely to have been published on these drugs prior to this date, given that the drugs were launched in 2007 (epoetin alfa [Binocrit®]) and 2009 (epoetin theta). All searches were also limited to English language papers, although some foreign language papers would have been identified by virtue of being included in other systematic reviews.

The following databases were searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); the Cochrane Library including CENTRAL, the Cochrane Database of Systematic Reviews, DARE, Health Technology Assessment (HTA), National Health Service Economic Evaluation Database (NHS EED) and Health Economic Evaluation Database (HEED); Web of Science (Thomson Reuters); CINAHL (EBSCO); British Nursing Index (ProQuest); Health Management Information Consortium (HMIC) (Ovid); Current Controlled Trials; Clinical Trials.gov; U.S. Food and Drug Administration (FDA) website; European Medicines Agency website (EMA) website.

See Section 4.1.1 in the assessment report for additional websites searched for background information.

The database search results were exported to, and de-duplicated using Endnote (X5). De-duplication was also performed using manual checking. The search strategies and the numbers retrieved for each database are detailed in Appendix B in the assessment report. After the reviewers completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies.

A supplementary search was carried out in MEDLINE (Ovid) to search for utilities as a function of haemoglobin (Hb) levels and for information on Hb levels after chemotherapy ends. A systematic search was not required for this part of the review so the search strategy was limited to MEDLINE. These searches are detailed in Appendix B in the assessment report.

Wilson and Colleagues, 2007†

Studies included in the previous HTA review (Wilson and colleagues, 2007)† were screened versus the inclusion criteria for the PenTAG review for includable studies.

Reference Lists

Reference lists of included guidelines, systematic reviews, and clinical trials were scrutinised for additional information.

Ongoing Trials

A search for ongoing trials was also undertaken. Terms for the intervention ("epoetin" OR "darbepoetin") and condition of interest (cancer* OR carcinoma* OR leukemia OR malignan* OR neoplasm* OR tumo?r OR myelo* OR lymphoma* OR oncolog* OR chemotherapy*) were used to search the following trial registers: ClinicalTrials.gov and Controlled Trials (ISRCTN) for ongoing trials. Trials that did not relate to cancer-induced or chemotherapy-related anaemia were removed by hand-sorting. Finally, duplicates, identified via their study identification numbers where possible, were removed. Searches were carried out on 28 August 2013.

Eligibility Criteria

Study Design

Only RCTs were included. Non-randomised trials and quasi-randomised trials (such as where allocation is based on date of birth or day of month) were excluded.

Population

People had to be receiving chemotherapy for solid tumours, malignant lymphoma, or multiple myeloma (and people with non-myeloid malignancies), at risk of transfusion as assessed by general status (e.g., cardiovascular status, pre-existing anaemia at the start of chemotherapy), and non-myeloid malignancies. There were no age restrictions; however, it is recognised that the licenses for all the interventions of interest do not cover erythropoietin use in children for this indication. Studies where erythropoietin was given in the context of myeloablative chemotherapy ahead of bone marrow or peripheral blood stem cell transplantation, or for short-term preoperative treatment to correct anaemia or to support collection of autologous blood before cancer surgery, were excluded.

Interventions

Studies evaluating the use of erythropoietin-stimulating agents (ESAs) were included if given to treat cancer treatment-induced anaemia. The ESAs of interest for this appraisal were: epoetin alfa (Eprex®, Binocrit®), epoetin beta (NeoRecormen®), epoetin theta (Eporatio®), epoetin zeta (Retacrit®), or darbepoetin alfa (Aranesp®).

Concomitant anaemia therapy such as iron or granulocyte colony-stimulating factor (G-CSF) supplementation was permitted, as was red blood cell transfusion (RBCT). However, G-CSF had to be administered to patients in both the treatment and control arms.

Dose

ESA administration varied considerably among the published literature. Variation with respect to: Hb levels (trigger [the point below which ESAs should be administered, ≤10.0 g/dL]; and targeted [the point above which ESAs should be stopped or titrated, 10–12 g/dL]); dose escalation (used if people do not achieve a haematological response within a specified time period); abandonment for persistent non-responders; and, duration of use following each chemotherapy session. The majority (82%) of studies were initiated before the 2008 update of the Summary of Products Characteristics (SPCs) and no studies were completely aligned with the UK marketing authorisation for these drugs in respect of these criteria (see Appendix C in the assessment report).

For the main analysis for this systematic review, studies were considered eligible for inclusion if they used a licensed start dose regardless of how they dealt with other criteria stipulated by the license. Thus, ESAs administered weekly, for epoetin alfa and epoetin zeta to be administered three-times weekly, for epoetin beta to be administered three to seven times per week; and, for darbepoetin alfa to be administered every three weeks. Fixed (epoetin theta) and weight-based (epoetin alfa, epoetin beta, epoetin zeta, and darbepoetin alfa) dosages were allowed.

In addition the Assessment Group also considered inclusion Hb criteria as closer to licence ≤11 g/dL and >11 g/dL; and target Hb as closer to licence ≤13 g/dl and >13 g/dl.

Comparator

The main comparators of interest were: placebo, best supportive care (including adjustment to the cancer treatment regimen, blood transfusion, and iron supplementation). In addition, the comparator could be one of the other ESAs under consideration, provided it was administered in line

with the relevant marketing authorisations.

Outcomes

Outcomes sought from the studies fell into four categories: anaemia-related outcomes, malignancy-related outcomes, adverse events data and patient-specific outcomes such as quality of life outcomes and patient's preferences.

Refer to Section 4.1.2.5 in the assessment report for more information on outcomes.

Selection of Studies

Studies retrieved from the update searches were selected for inclusion according to the inclusion/exclusion criteria specified above. First, titles and abstracts returned by the search strategy were screened for inclusion independently by two researchers. Disagreements were resolved by discussion, with involvement of a third reviewer. Full texts of identified studies were obtained and screened in the same way. Abstract only studies were included provided sufficient methodological details were reported to allow critical appraisal of study quality. In addition, studies included in the review conducted by Wilson and colleagues (2007)† were screened for inclusion against the eligibility criteria for this review.

Eligible studies were then re-screened to apply the inclusion criteria "intervention administered in accordance with their licensed indications". For this systematic review, this was defined as a licensed start dose irrespective of how the study dealt with other criteria stipulated by the license. Thus, ESAs administered weekly, for epoetin alfa and epoetin zeta to be administered three-times weekly, for epoetin beta to be administered three to seven times per week; and, for darbepoetin alfa to be administered every three weeks. Fixed (epoetin theta) and weight-based (epoetin alfa, epoetin beta, epoetin zeta, and darbepoetin alfa) dosages were allowed.

Assessment of Quality-of-Life

See Section 5 of the assessment report for information on the assessment of quality-of-life.

Assessment of Cost-effectiveness

Systematic Review of Existing Cost-effectiveness Evidence

Wilson and Colleagues (2007)†: Summary

A systematic review of cost-effectiveness evidence was reported by Wilson and colleagues (2007)† which informed previous NICE guidance. See Section 6.1.1 in the assessment report for details of the literature search.

Update Review

Searches

Search strategies were designed by an information specialist and were based on the searches for clinical effectiveness evidence, with additional terms to limit to economic evaluations (see Appendix B in the assessment report). The table below gives a summary of the databases searched. Where possible, searches were limited to publications since 2004.

Table. Databases Searched in the Update Review

Database	Host	Date Range
MEDLINE	Ovid	1946 to May week 3 2013
MEDLINE In-Process & Other	Ovid	To 28 May 2013
Non-Indexed Citations		
EMBASE	Ovid	1980 to 2013 week 21
NHS EED	Cochrane library	Issue 2 of 4, April 2013
Web of Science	Thomson Reuters	Searched 29/05/2013
CINAHL	EBSCO	Searched 29/05/2013
OHE HEED	Cochrane library	Searched 29/05/2013
Key: NHS EED, National Health Service Economic Evaluation Database; OHE EED, Office of Health Economics Health Economic		

Database	Evaluations Database	Host	Date Range
Note: A date filter term was used to specify publication date from 2004 (except for OHE HEED)			

In addition, supplementary searches not limited to cost-effectiveness were conducted in the following databases on 24–30 May 2013 (see Appendix B in the assessment report)

- Cochrane Database of Systematic Reviews (via the Cochrane Library): Issue 4 of 12, April 2013
- Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database (via the Cochrane Library): Issue 2 of 4, April 2013
- Health Management Information Consortium (HMIC) database (via Ovid): 1979 to March 2013.

Screening

Inclusion and exclusion criteria were the same as for the clinical effectiveness systematic review with the following exceptions (as specified in the appraisal protocol):

- Non-randomised studies were included (e.g., decision model based analyses or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost consequence analyses were included. (Economic evaluations which only report average cost-effectiveness ratios were only included if the incremental ratios could be easily calculated from the published data).
- Stand-alone cost analyses based in the UK NHS were also sought and appraised.

Titles and abstracts were screened for relevance by two reviewers, with disagreements resolved by discussion. Full texts were retrieved for references judged to be relevant and were screened for eligibility by the same reviewers, with disagreements resolved by discussion.

The bibliographies of review articles not judged eligible for inclusion were examined by one reviewer to identify other potentially relevant references. These references were retrieved and checked for eligibility in the same way as full texts from database searches.

See Section 6.1 and Appendix B in the assessment report for further details of the literature search for cost-effectiveness.

†â€‹Wilson J, Yao GL, Raftery J et al. (2007). A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess. 11, 1-202, iii-iv.

Number of Source Documents

Assessment of Clinical Effectiveness

See Section 4.2.1 and Figure 1 in the assessment report (see the "Availability of Companion Documents" field) for information on studies identified and included.

Assessment of Cost-effectiveness

See Section 6.1.2.3. and Figure 28 in the assessment report for information on studies identified and included.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Data Extraction and Management

Included full papers were split between four reviewers for the purposes of data extraction using a standardised data extraction form, and checked independently by another reviewer. Discrepancies were resolved by discussion with the involvement of an additional review team member if necessary. Information extracted and tabulated included details of the study's design and methodology, baseline characteristics of participants, and results including health-related quality of life (HRQoL) and any adverse events (AEs) if reported (see Appendix D in the assessment report).

If several publications for one study were identified, the data from the most recent publication were evaluated and amended with information from other publications.

For studies comparing more than one experimental arm to one control arm, the Assessment Group assigned a separate reference for each study arm with the author and publication year of the main publication and added the suffixes a; b. Due to this referencing system a study may appear more than twice in the list of included studies.

Where there was incomplete information on key data, the Assessment Group referred to the 2012 Cochrane Review. For the update of the Cochrane Review the authors evaluated documents presented at the Oncology Drug Advisory Committee (ODAC) hearing at the U.S. Food and Drug Administration (FDA) held in May 2004, May 2007, and May 2008. These documents were reported to include briefing documents plus additional Powerpoint presentations prepared by medical review authors of the FDA, as well as documents and additional Powerpoint presentations prepared by the manufacturers.

Critical Appraisal

Four reviewers independently assessed quality for the newly identified studies (2004 onwards) (see Table 9 in the assessment report).

Methods of Data Analysis/Synthesis

Where data permitted the results of individual studies were pooled using the methods described below.

A random-effects model was assumed for all meta-analyses. For binary data, risk ratio (RR) was used as a measure of treatment effect and the DerSimonian–Laird method was used for pooling. For continuous data, mean differences were calculated if the outcome was measured on the same scale in all trials. For QoL only identical scales and sub-scales were combined in a given meta-analysis. For time-to-event data; i.e., overall survival (OS), data were extracted from the Cochrane review. In the Cochrane review hazard ratios (HRs) were based on individual patient data (IPD); where IPD were not available, the HR was calculated from published reports including secondary analyses or binary mortality data. Similarly, data from the Cochrane review were used for mean haemoglobin (Hb) change, transfusion requirement, mean units of blood transfused, complete tumour response, QoL, and AEs, if this information was not available in the published trials' reports.

One study had two intervention arms that were separately compared with the control arm. To take account of the fact that some study-specific estimates would use the same control arm, the information was divided across the number of comparisons from the study. When pooling RRs, the number of events and the total sample size in the control arm were divided equally across the comparisons, and when pooling mean differences the total sample size in the control arm was adjusted and divided equally across the comparisons. However, if only one experimental arm was eligible for the analysis all participants assigned to the control arm were included.

Pre-specified subgroup analyses were conducted, if appropriate. In addition based on subgroup analyses, meta-regression models were conducted including random effect and a subgroup as a covariate to assess the effects of subgroups on the outcomes. These analyses were

conducted if there was sufficient number of studies in each subgroup. The DerSimonian-Laird method was used to estimate between-study variance in meta-regression. All covariates showing a significant effect ($p<0.05$) in a univariate analysis were further considered in a model selection. However, these analyses have to be interpreted with caution as they can only be exploratory, and should be considered as hypothesis generating rather than hypothesis testing analyses.

See Section 4 in the assessment report for more information on methods of analysis/synthesis and specific subgroup analysis.

Assessment of Quality-of-Life

See Section 5 in the assessment report for information on the assessment of quality-of-life.

Assessment of Cost-effectiveness

Systematic Review of Existing Cost-Effectiveness Evidence

Wilson and Colleagues (2007)†: Summary

Included studies were critically appraised using the checklist suggested by Drummond and colleagues. Single points were also assigned to all but one criteria on the Drummond checklist when met and summed to give an overall quality score for a study.

Data were abstracted from the studies using a framework used by the West Midlands group in previous technology appraisals. Data abstraction was performed by one reviewer and checked by another.

Qualitative analysis was performed by one reviewer based on manually identified patterns in tabulated data. Conclusions were scrutinised by two other reviewers.

Update Review

Data Extraction

Study characteristics and results were abstracted by one reviewer using a template adapted from the systematic review by Wilson and colleagues (2007)†. In addition, parameters which could be used in the construction of an independent economic model were identified and noted.

Selection of Studies for Detailed Appraisal and Reporting

Data extraction was conducted for all included studies, but for reasons of expediency, not all studies which were eligible according to the inclusion and exclusion criteria were selected for detailed appraisal and reporting. Instead, only systematic reviews (n=2) and cost-utility studies (n=3) were selected for detailed appraisal and reporting. Data extraction for these studies was checked by a second reviewer.

Quality Appraisal

Selected studies (all new systematic reviews and cost-utility studies) were quality assessed by one reviewer. In line with the instructions accompanying the final checklist, where there was insufficient information available in the article to assess quality the item was marked "No". In contrast to the previous review there was no attempt to assign scores to studies on the basis of the quality appraisal checklist. Where these studies were based on decision models, they were further quality assessed.

Analysis

The results of included studies were qualitatively analysed on the basis of visual inspection of the tabulated extracted data. Draft conclusions were drawn by one reviewer and scrutinised by all authors from PenTAG.

See Section 6 in the assessment report for more information on the economic literature analysis.

Independent Economic Assessment

Model Structure

In the PenTAG assessment, the economic evaluation takes the form of a simple, empirical model, informed directly by the systematic review of clinical effectiveness. This differs from standard mechanistic modeling approaches (such as Markov or discrete event simulation models), which require specific states and processes to be modelled.

The model compares patients receiving erythropoietin-stimulating agent (ESA) therapy to patients not receiving ESA therapy (referred to as the ESA arm and control arm from here) and is split into two temporal sections, one to evaluate the short-term costs and quality-adjusted life years

(QALYs) (while patients are anaemic) and one to evaluate long-term QALYs.

Short-term costs are accrued in the form of ESA drug acquisition and administration, red blood cell transfusion costs and costs of adverse events. Although patients may incur significant costs through cancer treatment (e.g., chemotherapeutic agents) these costs are not modelled as they are assumed to be equal for the ESA and control arms. Short-term QALYs are accrued as health-related quality of life (HRQoL) is improved by ESA therapy correcting anaemia and associated symptoms (e.g., fatigue); no difference in time spent in the short-term phase is modelled between the arms.

Long-term QALYs are accrued due to potential differences in overall survival between the two arms; it is assumed that HRQoL is equal for both arms in this phase as patients no longer have cancer treatment-induced anaemia and HRQoL is driven by symptoms of cancer. Although patients may incur significant ongoing costs related to cancer treatment (e.g., costs of maintenance chemotherapy, subsequent chemotherapy cycles or relapse), as these are highly uncertain (due to the wide range of cancers patients may have and the treatments for them) and because the inclusion of such costs could perversely worsen cost-effectiveness for the arm with greater overall survival, these costs are not modelled in the base case.

See Section 7 in the assessment report for additional information about the independent economic assessment.

*†Wilson J, Yao GL, Raftery J et al. (2007). A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess. 11, 1-202, iii-iv.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS

and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee concluded that it was reasonable for the Assessment Group to assume in the economic analysis that all erythropoiesis-stimulating agents (ESAs) offer the same effectiveness.

The Committee also concluded that the treatment duration and haemoglobin concentrations assumed in the model were appropriate.

The Committee was generally satisfied with the Assessment Group's approach to estimating the utility values but concluded that the quality-adjusted life year (QALY) gain with ESAs may have been underestimated.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee was concerned that the Assessment Group did not include disutilities associated with adverse reactions in the QALY calculation given that most adverse reactions occurred more frequently in the ESA arms. However, it recognised that there would be minimal effect on incremental cost-effectiveness ratios (ICERs) given that the adverse reactions in the studies were rare.

The Committee concluded that there was not enough evidence to suggest a survival gain with ESAs and therefore agreed that the model should incorporate a hazard ratio of 1 instead of 0.97.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee concluded that the QALY gain with ESAs may have been underestimated given that the potential benefits of ESAs associated with avoiding blood transfusions and reducing the need for hospital visits were not captured in the QALY calculation.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

The Committee concluded that using ESAs only at starting haemoglobin concentrations that reflect the marketing authorisations would slightly reduce the base-case ICERs.

What Are the Key Drivers of Cost-effectiveness?

The Committee noted that the prices of the drugs and the assumption that ESAs prolong survival most strongly influenced the cost-effectiveness results.

Most Likely Cost-effectiveness Estimate (given as an ICER)

The Committee concluded that the scenario assuming equal survival and using contract prices was the most plausible. It noted that the probabilistic ICERs for this scenario were all below £30,000 per QALY gained and that the benefits of ESA treatment associated with avoiding blood transfusions and starting ESA treatment only at haemoglobin concentrations in line with the marketing authorisations would likely reduce the ICERs. The Committee agreed that the most plausible ICER was below £20,000 per QALY gained.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the Technology Assessment Group (TAG). The main clinical effectiveness evidence came from randomised controlled trials. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the TAG.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- The clinical expert highlighted that erythropoiesis-stimulating agents (ESAs) lower the need for transfusions, but are not widely used in the UK for treating anaemia in people having chemotherapy.
- The Committee heard from the patient expert that ESAs are highly valued by patients, because they reduce the need for blood transfusions and improve quality of life.

Potential Harms

- The summary of product characteristics for Eprex and Binocrit (epoetin alfa) lists headache, nausea and pyrexia as very common adverse reactions, and deep vein thrombosis, hypertension, pulmonary embolism, diarrhoea, vomiting, rash, arthralgia and flu-like illness as common adverse reactions in patients with cancer.
- The summary of product characteristics lists the following common adverse reactions for epoetin beta in patients with cancer: hypertension, thromboembolic event and headache.
- The summary of product characteristics lists the following common adverse reactions for epoetin theta in patients with cancer: headache, hypertension, skin reactions, arthralgia and flu-like illness.
- The summary of product characteristics for epoetin zeta lists headache as a very common adverse reaction, and stroke, dizziness, deep vein thrombosis, an increase in blood pressure, pulmonary embolism, non-specific skin rashes, joint pains, flu-like symptoms, feeling of weakness and tiredness as common adverse reactions in patients with cancer.
- The summary of product characteristics for darbepoetin alfa lists hypersensitivity and oedema as very common adverse reactions, and hypertension, thromboembolic events (including pulmonary embolism), rash, erythema and injection-site pain as common adverse reactions in patients with cancer.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has anaemia associated with cancer treatment and the doctor responsible for their care thinks that erythropoiesis-stimulating agents (ESAs) are the right treatment, it should be available for use, in line with NICE's recommendations.
- The NHS procures ESAs on a 'price-volume' agreement on a confidential basis with the companies. The contract prices used for the decision-making in this appraisal represent the latest tenders to London hospitals provided for this appraisal by the Commercial Medicines Unit and the South East England Specialist Pharmacy Services to NICE. Any enquiries from NHS organisations about the contract prices used in this appraisal should be directed to the Commercial Medicines Unit and the South East England Specialist Pharmacy Services.
- NICE has developed tools to help organisations put this guidance into practice (listed below).
    - Costing template and report to estimate the national and local savings and costs associated with implementation.

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142). London (UK): National Institute for Health and Care Excellence (NICE); 2014 Nov. 47 p. (Technology appraisal guidance; no. 323).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2008 May (revised 2014 Nov)

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

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National Institute for Health and Care Excellence (NICE)

Guideline Committee

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 36 p. (Technology appraisal guidance; no. 142)

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer receiving chemotherapy (including review of TA142). Costing report. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Nov. 12 p. (Technology appraisal guidance; no. 323). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer receiving chemotherapy (including review of TA142). Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Nov. (Technology appraisal guidance; no. 323). Electronic copies: Available from the NICE Web site .
- Crathorne L, Huxley N, Haasova M, Snowsill T, Jones-Hughes T, Hoyle M, Briscoe S, Coelho H, Long L, Medina-Lara A, Mujica-Mota R, Napier M, Rudin C, Scatchard K, Hyde C. The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model. Assessment report. Exeter (UK): Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School; 2014. 746 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142). Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Nov. 3 p. (Technology appraisal guidance; no. 323). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site . Also available in Welsh from the NICE Web site .

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NGC Status

This NGC summary was completed by ECRI Institute on August 8, 2008. This summary was updated by ECRI Institute on April 1, 2010 following the U.S. Food and Drug Administration advisory on Erythropoiesis-Stimulating Agents (ESAs). This summary was updated by ECRI Institute on March 2, 2015.

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